Universitätsspital Zürich
Klinik für Neurochirurgie
Direktor: Prof. Dr. med. L. Regli

Long-term follow-up of patients operated on low-grade brainstem glioma in Zurich between 1963 and 2007

Inaugural-Dissertation
zur Erlangung der Doktorwürde der Medizinischen Fakultät
der Universität Zürich

Vorgelegt von
Wael Khaled Ibrahim Abou Hadeed
von Fribourg FR

Genehmigt auf Antrag von Prof. Dr. med. L. Regli
Zürich 2015

Index

1. Abstract

Objective: To present the long-term follow-up results after brainstem glioma (BSG) surgery at the University Hospital Zurich including low-grade gliomas (LGG) over more than 4 decades and to trace historical changes in BSG surgery with a special focus on LGG.

Methods: I searched the archives of the neurosurgery department for BSG surgeries including LGG between 1937 and 2007. The directors of the department in this time span were the surgeons H. Krayenbühl, G. Yasargil and Y. Yonekawa. Histological information was added from the department of pathology. Follow-up data was completed from the community registration offices and patient records in the department of neurosurgery.

Results: In total I found 124 patients with BSG surgeries in the data collection including 64 patients with LGG. The median age at surgery was lower in the era Yasargil (18y, N=77) than in the era Yonekawa (30y, N=27, p = 0.02). Operated LGG patients were higher presented in the era of Yasargil than in the era Yonekawa (53/77 *vs.* 13/27, crosstabulation chi2 p=0.055). Follow-up (FU) of the LGG patient group was available in 47 patients (73.4%) with a median of 9 years (range 0-33years). 18 patients (38%) had a FU >10 years and 10 patients (21.3%) a long-term FU >20 years. There was only one documented death in one patient 27 years after surgery. Median progression free survival (PFS) was 27 years with no significant difference between patients operated in the era Yonekawa (median PFS 6 years) or Yasargil (median PFS 27 years) (p=0.387).

Conclusion: In this study we were able to demonstrate long-term FU with a high overall survival and PFS in LGG patients after BSG surgery. As the University Hospital Zurich was among the first to initiate BSG surgery, we could trace the paradigms of BSG surgery from its onset in a single center study.

2. Introduction

Brainstem gliomas (BSG) constitute approximately 1% of adult brain tumors and 10% of all pediatric brain tumors and are the most common neoplasm occurring in the brainstem.[1] BSG have historically been one of the most difficult cancers to treat and were once uniformly discounted as surgically unresectable lesions.[2] In the times before computed tomography (CT), magnetic resonance imaging (MRI) these lesions were summarized as malignant tumors regardless of specific histology due to their location itself.[3] Starting in 1980 several groups reported their surgical experiences in BSG surgery and classifications were introduced to display tumor types benefiting from surgery.[4-8] Besides histological classifications including malignant BSG – with a comparable dismal prognosis to other intracerebral high-grade gliomas – and low-grade BSG – with a more favorable course –morphological subtypes can be differentiated.[5-7] For instance, two growth types of brainstem tumors, diffuse and circumscribed are described in the literature.[6-8] In both types patients often present with incongruously minor deficits, even with large tumors, until the late stages of the illness, when the condition deteriorates rapidly.[9] The mean age of diagnosis in BSG is 7-9 years, and there is no age or sex predilection.[10, 11] A second peak appears at the fourth decade of age, however adult BSG are more uncommon and poorly understood with respect to prognostic factors.[1, 12]

Since our department was one of the first hospitals worldwide, which treated BSG surgically we were interested in the paradigm changes of BSG surgery over the last decades and the long term follow-up of the operated patients. To provide a more consistent and comparable analysis about BSG surgery we included only patients with an available histopathological diagnosis and patients with low-grade gliomas (LGG) to provide long-term outcome data after BSG surgery.

3. Patients and Methods

Three chairmen presided over the Department of Neurosurgery at the University Hospital Zurich between 1937 and 2007 and performed surgery on BSG, which were included in this study: H. Krayenbühl (1937 - 1973), G. Yasargil (1973 - 1993) and Y. Yonekawa (1993 - 2007). Analyzing all patient records that have been operated on BSG at the Department of Neurosurgery at the University Hospital Zurich, I included only patients with 1) a histopathological diagnosis and 2) with the diagnosis of a LGG to the final analysis. Patients, which underwent biopsy only, were excluded. Patients in the era before CT or MRI, but with histopathology were included in this study. The retrospective data collection for this study was approved by the Institutional Review Board Zurich (KEK 2011-0069/3). Data concerning patient characteristics, tumor pathology and tumor location was obtained from the following sources:

1. The hardcopy archive of the Department of Neurosurgery. Patients' names from 1937 – 1997 are sorted according to tumor location.
2. The digitized surgery registry of the Department of Neurosurgery (in-house database) from 1996 – 2007.
3. The digitized patient records of the University Hospital Zurich from 1990 – 2007. Patients search was based on ICD-10 codes that included C71-7 (neoplasm of the brainstem).
4. The tumor data base of the Institute of Neuropathology (1982 – 2007)

For overall survival (OS) analysis I collected data from the community registration offices of the largest municipalities of the patient recruitment area (Zurich, Winterthur,

Buelach and Uster). Histological diagnosis of the patients was obtained from the database of the Institute of Neuropathology, University Hospital Zurich for this study.

The surgeries were grouped with respect to the eras of the directors of the clinic: Krayenbühl (1937 - 1973), Yasargil (1973 - 1993) and Yonekawa (1993 - 2007). The data was analyzed and displayed with the program package MATLAB (www.mathworks.com). The equality of medians was tested by the Wilcoxon rank sum test, the cross-tabulation by chi2 test. Statistical significance was assumed for $p<0.05$.

4. Results

Low-grade brainstem glioma patients

Out of the 88 patients with available histopathology, there were 64 low-grade glioma (73%) patients including 35 male (54.7%) and 29 (45.3%) female patients with a median age of 19 years (mean 20.8, range 3-44) and a high proportion of children (age<16y) (n=25, 39%). Histopathological examination showed 55 low-grade astrocytomas (WHO grade I-II), 4 oligodendrogliomas, 2 ependymomas, 2 gangliogliomas and 1 oligoastrocytoma. A higher percentage of low-grade BSG were operated in the era Yasargil compared to the era Yonekawa (53/77 *vs.* 13/27, cross-tabulation chi2 p=0.055) and the most common tumor localization of the low-grade BSG was the pons in 28 cases (43.8%) and the mesencephalon in 27 cases (42.2%) followed by the medulla oblongata in 9 cases (14%). Loss to follow-up (FU) included 17 patients (26.6%) without any information after discharge of the patients after index surgery. Median last FU for the available 47 patients (73.4%) was 9 years (range 0-33years) including 18 patients (38%) with a follow-up longer than 10

years and 10 patients (21.3%) with a long-term follow-up over 20 years. (Figure 1)

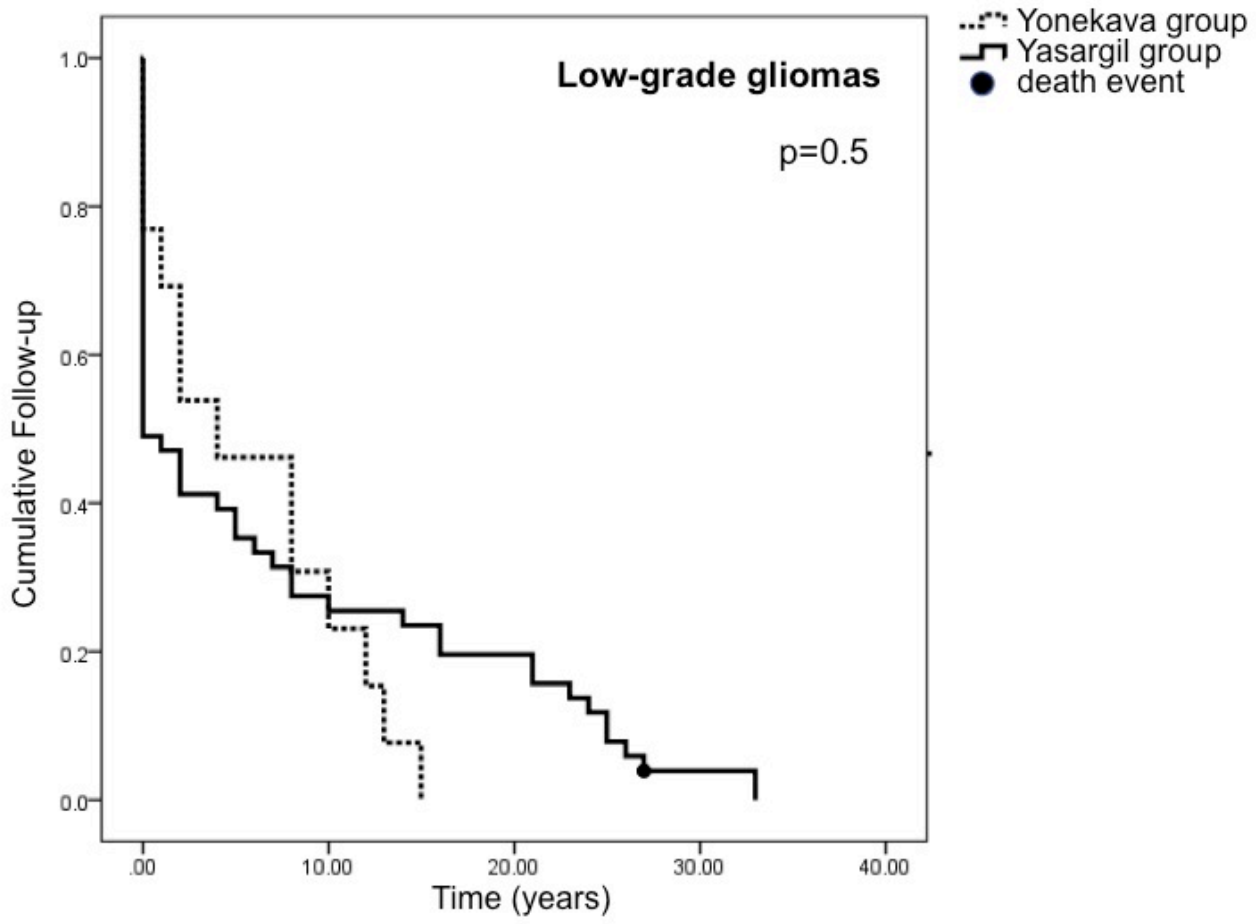

Figure 1. Cumulative long-term follow-up (Kaplan-Meier) for N = 64 patients with LGG grouped by era Yasargil and Yonekawa. There is no significant difference between both groups (p=0.5). The dot represents the only documented death in the Yasargil group.

There was only one documented death 27 years after surgery. All other 46 patients were alive at last follow-up some with long term postoperative MRI (Figure 2).

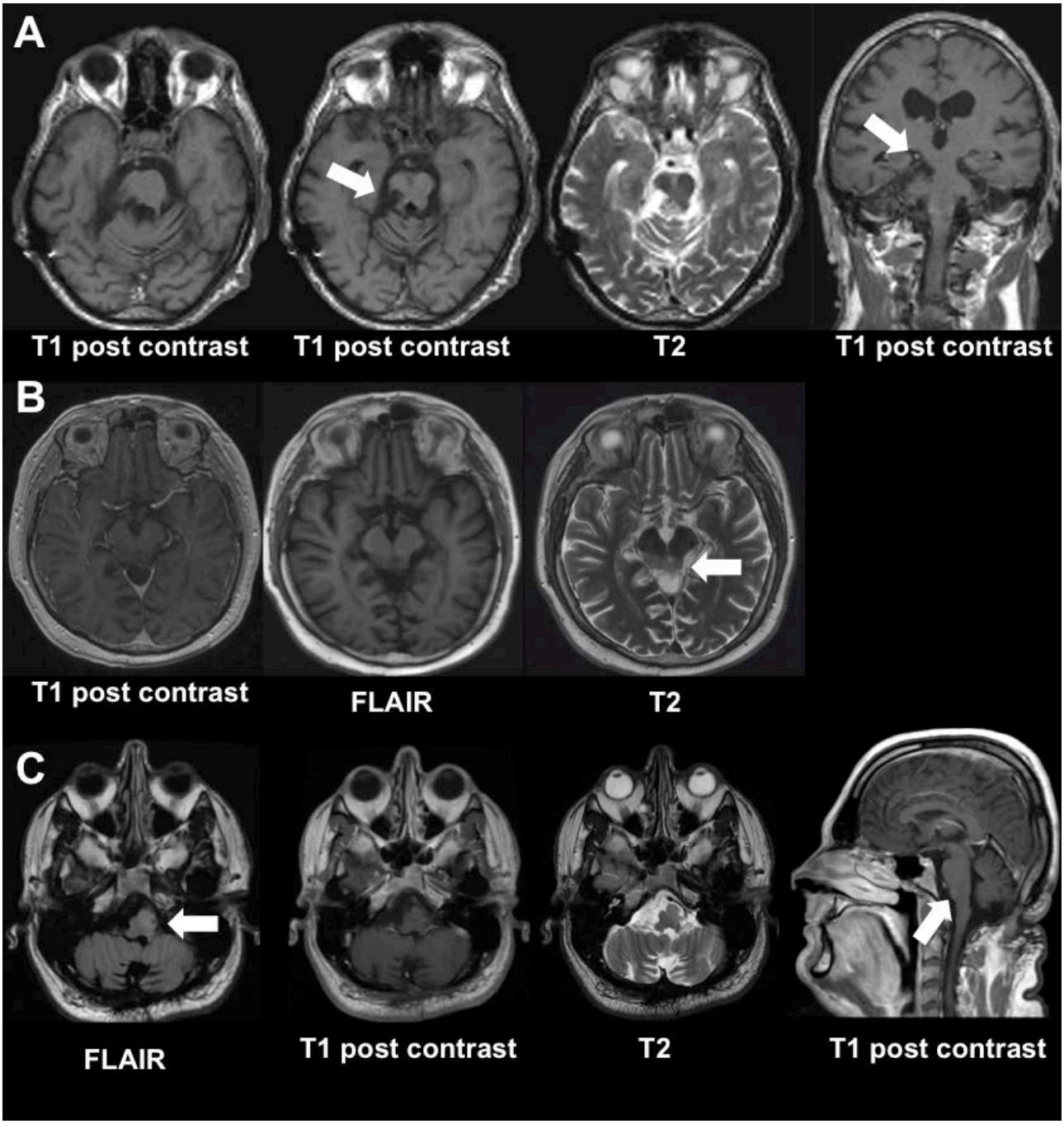

Figure 2. Follow-up MRIs examples of three long-time survivors with pilozytic astrocytomas (WHO grade I) all operated by Prof. Yasargil. **A**: 44y/m patient with a right pontomesencephalic lesion operated via a right-sided retrosigmoidal approach (06/1986), last follow-up MRI 25years after surgery shows a complete resection without recurrence and a residual left-sided hemiparesis (M4). **B**: 24y/m patient with dorsal mesencephalic astrocytoma subtotal resected via an infratentorial supracerebellar approach (11/1985), tumor remnant stable on last follow-up MRI 26years after

surgery, without any neurological deficit. **C**: 18y/m patient with a left-sided ventro-lateral lesion in the medulla oblongata. Gross total resection via a suboccipital median approach (04/1992). Tumor recurrence occurred 01/1993, since then tumor size was stable without treatment until last follow-up 19 years later. At last follow up the patient was without neurological deficits.

The survival status of the 17 patients, which were lost to follow-up after discharge, was unknown. Median progression free survival (PFS) of the 47 patients was 27 years with no significant difference between patients operated in the era Yonekawa (median PFS 6 years) or Yasargil (median PFS 27 years) (Figure 3). Recurrence or progression of a tumor rest was present in 29.4% patients (10/34) of the Yasargil group and in 30.8% patients (4/13) of the Yonekawa group.

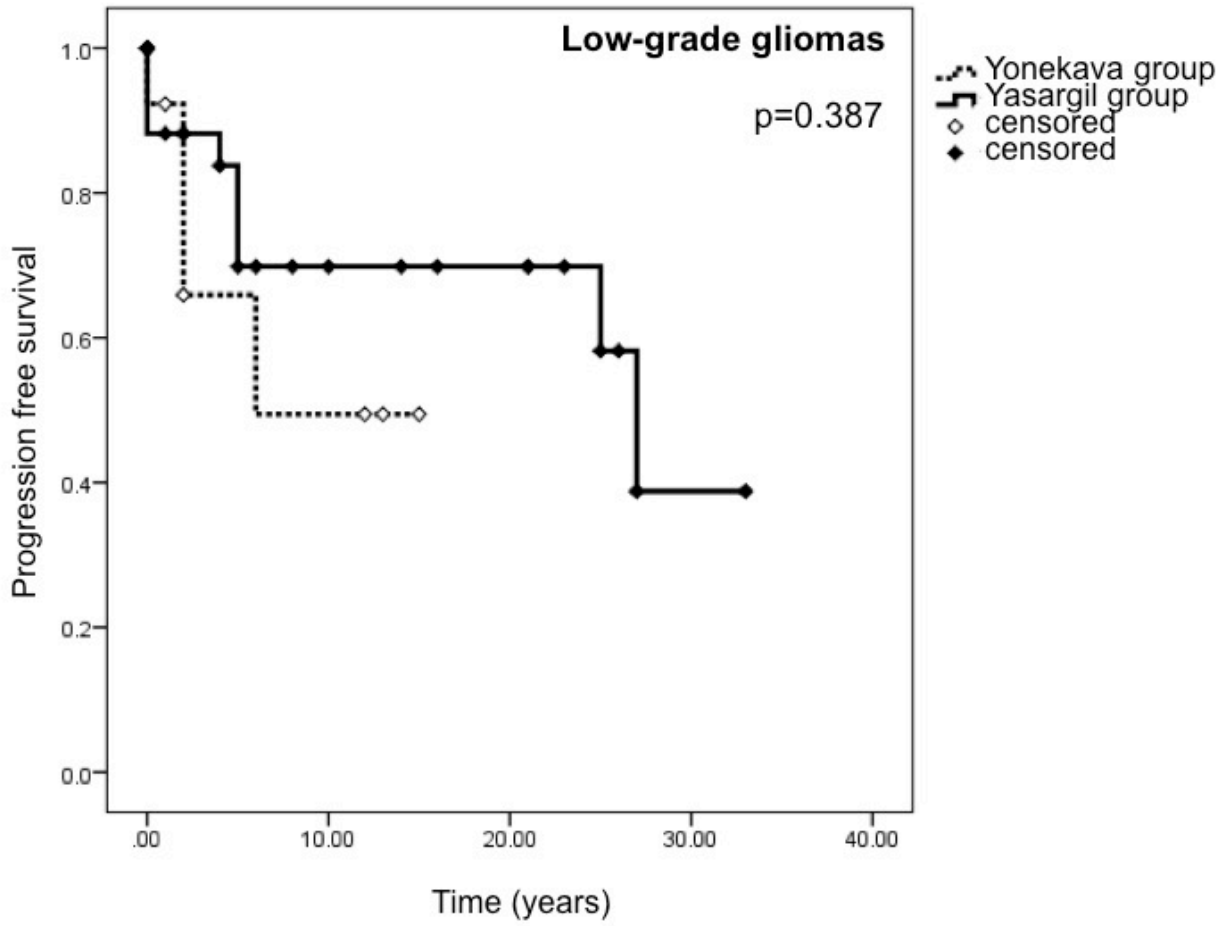

Figure 3. Progression-free survival (PFS) (Kaplan-Meier) for N = 64 patients with LGG grouped by era Yasargil (median PFS 27 years) and Yonekawa (median PFS 6 years).

There is no significant difference between both groups (p=0.387). Patients with no progression at last follow-up were censored.

Overall brainstem glioma patients

Including all brainstem surgeries 124 surgeries in 124 patients (68 male, 55%) were found in the data collection including 4 patients in the era Krayenbühl (4%), 77 patients in the era Yasargil (71%), and 27 patients in the era Yonekawa (25%) (Figure 4A). In 88

cases tumor histology of the glioma pathology group could be further specified. Median age was 20 years (mean 25, range 2-77years, n=104) with a median age of 18 years (range 3-64 years) in the era Yasargil and 30 years (range 2-77 years) in the era Yonekawa (p=0.02). Overall, 36% (n=37) of the patients were children (<16years) (Figure 4B and C), with a higher representation in the low-grade group (n=25/64, 39%) compared to the non low-grade group (n=12/40, 30%).

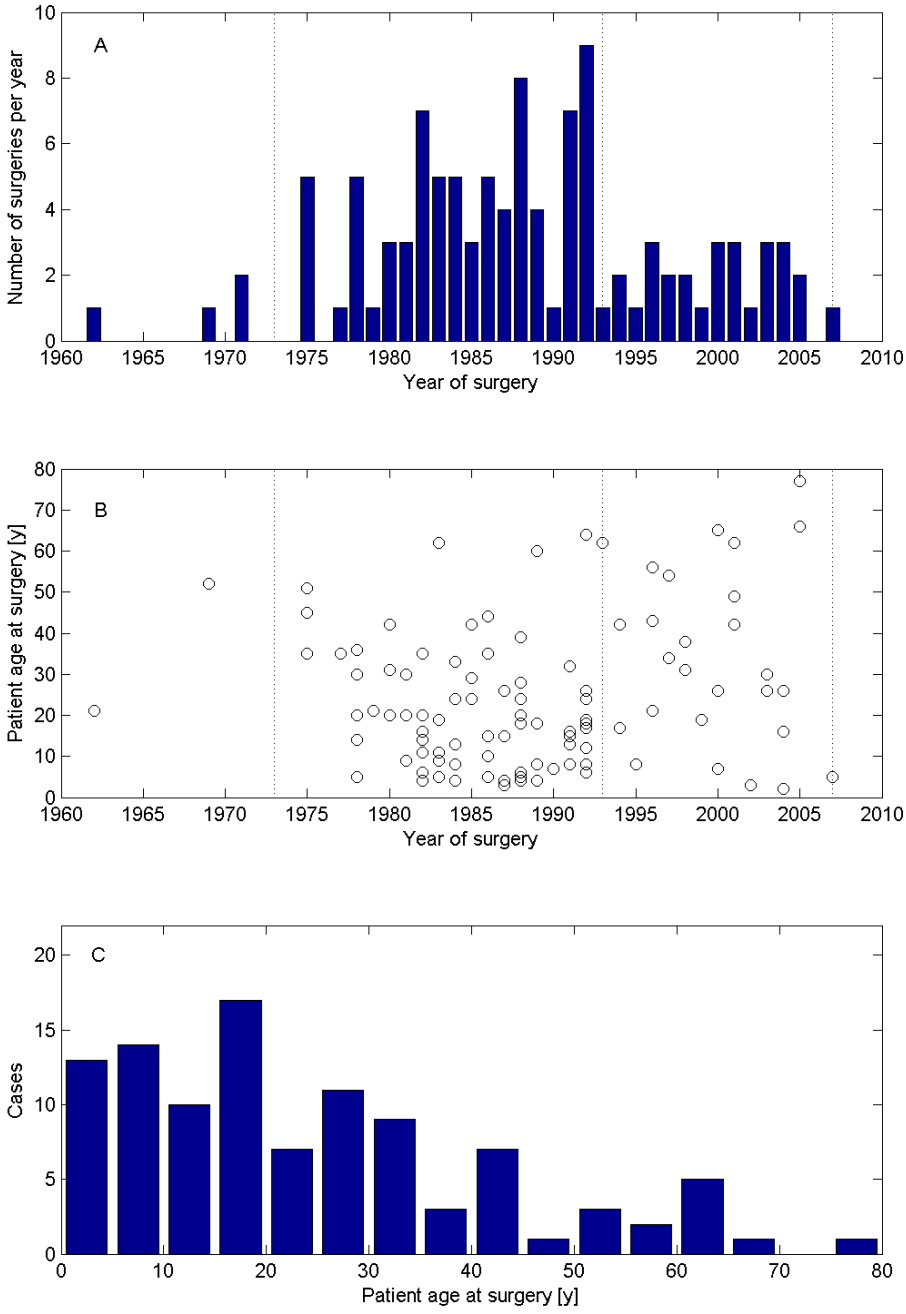

Figure 4. A Frequency of brain stem glioma surgeries. Era Yasargil (1973 - 1993) and era Yonekawa (1993 - 2007). **B** Age of each patient at surgery. **C** Age-distribution at surgery.

5. Discussion

As the most striking result we present here that survival after surgery for brainstem glioma may last for decades. This result is based on a BSG surgery series spanning 44 years from one of the first neurosurgical centers introducing microsurgery of the skull base. The pioneering work initiated by Dr. Krayenbühl and Dr. Yasargil and continued by Dr. Yonekawa stimulated neurosurgeons during their era until now.[13] In the Zurich BSG series a large number of patients were treated by Dr. Yasargil and – to a lesser extent – by Dr. Yonekawa. Children constitute a large portion of the patients operated on, especially in the LGG group, which is in concordance with the incidence peak in the current literature.[2, 14-16] Interestingly, the median patient age at surgery was significantly lower in the cohort of Dr. Yasargil than in the cohort of Dr. Yonekawa, which displays a more balanced age distribution (Figure 4C). An explanation for these findings might be found by the fact that in the beginning of the BSG surgery era patients and especially children were mainly operated to confirm the diagnosis and as a therapy modality itself. With novel imaging modalities such as MRI and a more detailed understanding in natural history and outcome of these lesions, the availability of treatment strategies for BSG changed over the last decades.[17, 18] For instance, diffuse intrinsic BSG are nowadays not recommended to be primarily surgically resected or biopsied, since surgery does not alter the treatment strategy.[18, 19] Based on modern MRI sequences, which allow a specific diagnosis of these lesions, the large group of diffuse intrinsic BSG are mainly treated conservatively with radiation therapy or chemotherapy.[20] Only a small amount of BSG (10-15%) needs to be surgically treated such as in the presence of a focal, enhancing mass in the midbrain, medulla, or peduncle, or the presence of a dorsally exophytic tumor protruding into the 4th

ventricle.[17] These results, therefore, reflect the changes in therapy management of BSG over the last decades.

Comparing the histopathological findings of the BSG between the era of Yasargil and Yonekawa confirm the paradigm change in the therapy management of BSG. While a large part of LGG patients were operated by Prof Yasargil (80%), LGG were only a small part of all surgically received BSG histology in the following decades. After the introduction of MRI these low-grade lesions could be detected more specific by imaging and a biopsy or surgery would not alter further therapy strategy. However, a recently published meta-analysis on stereotactic biopsies of brainstem tumors showed the importance of a present histology before adjuvant treatment, since more than 8% of patients were diagnosed with a nonneoplastic disease.[21] Therefore, a biopsy might be recommended to ensure the assumed histology by MRI.

The age distribution of the surgical treated adult patients, however, does not display the second peak at the fourth decade as reported for the incidence of BSG diagnosis. (Figure 4C)[1] This may indicate that adults are subjected to neurosurgical treatment at a lower rate than children in general. These lesions account for only 1%-2% of intracranial gliomas in adults.[22]

The BSG – both LGG and non LGG – in this data set were mainly located in the pons and mesencephalon, which is in concordance with the literature.[2, 20, 23] With regards to outcome 73.4% of the LGG patients could be followed-up after discharge with long-term FU including a high overall survival. The median FU was 9 years including a high percentage of patients with decadal FU (Figure 1). There was only one documented death 27 years after surgery and all other 46 patients were alive at last follow-up, which is compared to the literature.[20, 24] Also the median PFS of 27 years is comparable with the literature (Figure 2).

Klimo et al. reported a PFS of 25.1 years in their study in 51 surgically treated brainstem LGG.[24]

As a limitation of this study, which retrospectively analyzed patient records over the last 4 decades, information on individual patient parameters is scarce. Several of the patients were operated on before the advent of diagnostic tools like MRI and dramatic changes in operative instrumentation and technology took place over the 4 decades time span such as intraoperative neuromonitoring. Also, FU was available for only a small number of patients. This could be improved by a nation-wide death registry and/or a prospective patient registry. Also the patient number and information at last FU was too small to further analyze tumor relapse or to obtain reliable OS data. On the other hand, our retrospective analysis enabled us to study BSG surgery over a time span of 4 decades to trace paradigm changes in BSG surgery.

6. Conclusions

In this study we were able to demonstrate long-term FU with a high overall survival and progression free survival in LGG patients after BSG surgery. As the University Hospital of Zurich was among the first to initiate BSG surgery, we could trace the paradigms of BSG surgery from its onset in a single center study.

7. References

1. Kesari S, Kim RS, Markos V et al. Prognostic factors in adult brainstem gliomas: a multicenter, retrospective analysis of 101 cases. *J Neurooncol* 2008; 88:175-183.

2. Jallo GI, Biser-Rohrbaugh A, Freed D. Brainstem gliomas. *Childs Nerv Syst* 2004; 20:143-153.

3. Matson DD. Surgery of posterior fossa tumors in childhood. *Clin Neurosurg* 1968; 15:247-264.

4. Epstein F, McCleary EL. Intrinsic brain-stem tumors of childhood: surgical indications. *J Neurosurg* 1986; 64:11-15.

5. Alvisi C, Cerisoli M, Maccheroni ME. Long-term results of surgically treated brainstem gliomas. *Acta Neurochir (Wien)* 1985; 76:12-17.

6. Epstein F, Wisoff JH. Intrinsic brainstem tumors in childhood: surgical indications. *J Neurooncol* 1988; 6:309-317.

7. Hoffman HJ, Becker L, Craven MA. A clinically and pathologically distinct group of benign brain stem gliomas. *Neurosurgery* 1980; 7:243-248.

8. Stroink AR, Hoffman HJ, Hendrick EB et al. Transependymal benign dorsally exophytic brain stem gliomas in childhood: diagnosis and treatment recommendations. *Neurosurgery* 1987; 20:439-444

9. Yasargil MG. Microneurosurgery- in 4 Volumes. Thieme Medical Publishers, Inc, Stuttgart, New York, 1996.

10. Frazier JL, Lee J, Thomale UW. Treatment of diffuse intrinsic brainstem gliomas: failed approaches and future strategies. *J Neurosurg Pediatr* 2009; 3:259-269.

11. Leach PA, Estlin EJ, Coope DJ. Diffuse brainstem gliomas in children: should we or shouldn't we biopsy? *Br J Neurosurg* 2008; 22:619-624.

12. Guillamo JS, Monjour A, Taillandier L. Brainstem gliomas in adults: prognostic factors and classification. *Brain* 2001; 124:2528-2539.

13. Yasargil MG. Personal considerations on the history of microneurosurgery. *J Neurosurg* 2010; 112:1163-1175.

14. Hargrave D, Bartels U, Bouffet E. Diffuse brainstem glioma in children: critical review of clinical trials. *Lancet Oncol* 2006; 7:241-248.

15. Laigle-Donadey F, Doz F, Delattre JY. Brainstem gliomas in children and adults. *Curr Opin Oncol* 2008; 20:662-667.

16. Maria BL, Rehder K, Eskin TA et al. Brainstem glioma: I. Pathology, clinical features, and therapy. *J Child Neurol* 1993; 8:112-128.

17. Albright AL, Packer RJ, Zimmerman R et al. Magnetic resonance scans should replace biopsies for the diagnosis of diffuse brain stem gliomas: a report from the Children's Cancer Group. *Neurosurgery* 1993; 33:1026-1029; discussion 1029-1030.

18. Packer RJ, Nicholson HS, Johnson DL, Vezina LG (1991) Dilemmas in the management of childhood brain tumors: brainstem gliomas. Pediatr Neurosurg 17:37-43

19. Halperin EC, Wehn SM, Scott JW et al. Selection of a management strategy for pediatric brainstem tumors. *Med Pediatr Oncol* 1989; 17:117-126.

20. Jansen MH, van Vuurden DG, Vandertop WP et al. Diffuse intrinsic pontine gliomas: a systematic update on clinical trials and biology. *Cancer Treat Rev* 2012; 38:27-35.

21. Kickingereder P, Willeit P, Simon T, Ruge MI (2013) Diagnostic Value and Safety of Stereotactic Biopsy for Brainstem Tumors: A Systematic Review and Meta-analysis of 1480 Cases. *Neurosurgery 2013;* 72:873-882

22. Reyes-Botero G, Mokhtari K, Martin-Duverneuil N et al. Adult Brainstem Gliomas. Oncologist 2012;

23. Khatua S, Moore KR, Vats TS et al. Diffuse intrinsic pontine glioma-current status and future strategies. *Childs Nerv Syst* 2012; 27:1391-1397.

24. Klimo P Jr, Pai Panandiker AS, Thompson CJ et al. Management and outcome of focal low-grade brainstem tumors in pediatric patients: the St. Jude experience. J Neurosurg Pediatr. 2013 Mar;11(3):274-81. Epub 2013 Jan 4.

8. Acknowledgements

Writing this thesis was a great and very instructive experience for wich I am very thankful. I am greatly indebted to Prof. Dr. med. Bertalanffy for giving me the opportunity to write this thesis.

I would like to express my gratitude to my supervisor, PD Dr. Sarnthein, for his support, patience, and encouragement throughout this thesis. It is not often that one finds an supervisor that always finds the time for listening to the little problems and roadblocks that unavoidably crop up in the course of performing research. His technical and editorial advice was essential to the completion of this dissertation and has taught me innumerable lessons and insights on the workings of academic research in general.

My thanks also go to Dr. med. Burkhard, who helped me especially with the medical part of this work and in analyzing the data. He also provided many valuable comments that improved the contents of this dissertation.

Last, but not least, I would like to thank my parents, Khaled and Nagwa, and my older sister May for their support and encouragement during the past few years.